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Synthesis of Some New Hydrazones from Quinazolinone Moiety

Hiba Ameen AL-ALAAF
University of Mosul

Mohammed Ahmed AL-IRAQI
College Al-Noor University

Abstract: Methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (4) is one of the important heterocyclic compounds. It is used as a precursor to synthesis new derivatives of quinazolin-4-one moiety. The compound (4) was synthesized *via* a series of steps from anthranilic acid. The anthranilic acid was converted to its methyl ester (1) by esterification with methanol under acidic condition. The ester (1) was reacted with chloroacetyl chloride to produce methyl α-chloroacetamido benzoate (2). The chloro compound (2) was converted to the corresponding thiocyanato compound (3) by its reaction with ammonium thiocyanate. The thiocyanato compound (3) was cyclized to the target precursor (4) by boiling of compound (3) for 12 h. compound (4) was reacted with aromatic aldehydes under boiling condition to produce different hydrazones derivatives (5-12). The hydrazones compounds (5-12) were reacted with Chloroacetyl chloride to afforded the Azetedines compounds (13-20). The synthesized compounds were identified *via* the physical and spectral data.

Keyword: 2-Mercapto quinazolin-4-one, Methyl 2-chloroacetamido benzoate, Methyl anthranilate, Azetidene coumpounds, Hydrazones derivatives, Thiocyanato compound.

Introduction

Quinazolin-4(3)-one is one of most important nucleus in heterocyclic chemistry owing to its participation in building block enormous number of biologically active compounds, by incorporation of the quinazolin-4(3)-one nuclei with heterocyclic moieties, such as triazole, thiadiazole and oxadiazole moieties. These compounds have been enticing attention of medicinal chemists to find and design novel structures having pharmacological activity (Jaianand et al., 2009). Quinazolin-4(3H)-one derivatives showed diversity of biological activity such as analgesic, anti-inflammatory (Bhalla et al, 1993), anti-hypertensive, anti-histaminic, anti-cancer (Boyle et al, 1993), anti-tumor (Al-Omary et al, 2012), sedative, hypnotic and anti-microbial activity (Vogels, 1994), anti-leishmanial activity (Agarwal et al, 2009) and as anti-oxidant (Decker; 2008). So, the previous views encouraged us to synthesize novel compounds containing quinazolin-4(3H)-one nucleus incorporated with hydrazones moiety starting from methyl α-[(4-oxoquinazolin-2-yl)thio]acetate.

Experimental

Melting points were recorded on a Stuart melting point SMP30 apparatus and were uncorrected. IR spectra were recorded as neat using Bruker system 2000 FT.IR spectrophotometer. 1H NMR spectra on a Bruker DPX (400)

super conducting NMR Spectrometer (400 MHz) using CDCl3 or DMSO-d6 as solvents with TMS as internal standard.

Synthesis of Methyl Anthranilate

A solution of anthranilic acid (1mol, 14.7 g) in absolute methanol (250 ml) was cooled to 0-5 oC, then a concentrated sulfuric acid (20 ml) was added dropwise with stirring. After the addition was completed, the mixture was refluxed for 72 h. The volatile components were evaporated under reduced pressure. A cold water (100 ml) was added to the residue. The mixture was basified by dropwise addition of (5 %) sodium bicarbonate solution, then the resulted mixture extracted with (20 * 30 ml) dichloromethane. The organic layers were collected, dried over magnesium sulfate, then evaporated. The crude product was recrystallized from methanol to give red crystals in 85% yield: melting point 22-23 oC. IR spectrum (neat, ν Cm-1) 3369 (N-H), 1704 (C=O), 1604 (C=C), 1442 (CH3), 1245 (C-O). 1H NMR (DMSO-d6) (δ, ppm): 3.39 (s, 3H, CH3), 6.66 (s, 2H, NH2), 6.53 (t, 1H, H5), 6.79 (d, 1H, H3), 7.25 (t, 1H, H4), 7.71 (d, 1H, H6).

Methyl N-(α-chloroacetyl) Anthranilate

To a solution of methyl anthranilate (0.01mol, 1.52 g) in chloroform (50 ml), chloroacetyl chloride (0.012 mol, 1.36 g) and potassium carbonate (0.015 mol, 2.1 g) were added. The reaction mixture was refluxed for 12 h. the volatile material was evaporated under reduced pressure. The residue was washed thoroughly with water then with 5% sodium bicarbonate solution and finally with water. The resulted product was dried then recrystallized from ethanol to give white crystals, in 98% yield, m.p. 90-91 oC, IR (neat, ν, cm -1): 3194 (N-H), 1682, 1676 (2C=O), 1441 (CH3),1226 (C-O). 1H NMR (DMSO-d6): δ, ppm, 3.89 (s, 3H, CH3), 4.45 (s, 2H, CH2), 7.27 (t, 1H, H5) , 7.66 (t, 1H, H4), 7.99 (d, 1H, H3), 8.40 (d, 1H, H6), 11.33 (s,1H, NH).

Synthesis of Methyl α-[(4-oxoquinazolin-2-yl)thio]Acetate

To a solution of methyl 2-(α-chloroacetamino) benzoate (2) (0.01 mol, 2.27 g) in methanol (30 ml), ammonium thiocyanate (0.015 mol, 1.15 g) was added with stirring. The mixture was refluxed for 12h then cooled to room temperature. The resulted precipitate was filtered off, washed with water, dried then recrystallized from methanol to give pale yellow crystals in 98 % yield, m.p. 191-192 oC. IR (neat, ν/cm -1): 3170 (N-H), 1734, 1682 (2C=O), 1375 (CH3), 681 (C-S). 1H NMR (DMSO-d6): δ, ppm: 3.69 (s, 3H, CH3), 4.11 (s, 2H, CH2), 7.4 (t,1H, H6), 7.75 (t, 1H, H7), 7.98 (d, 1H, H5), 8.23 (d, 1H, H8), 11.14 (s,1H, NH).

Synthesis of α-[4-oxoquinazolin-2-yl) thio]Acetohydrazide

A solution of methyl α-(4-oxoquinazolin-2-yl) thio] acetate (3) (0.01mol, 2.64 g), hydrazine hydrate (99.5 %) (0.015 mol, 0.75 g) in absolute ethanol (30 ml) was refluxed with stirring for 12 h. The solid product was separated by filtration, washed with cold water, dried, then recrystallized from ethanol to give green crystals in 90 % yield, m.p. 248 oC. IR (neat, ν, cm-1): 3289, 3128 (NH2, N-H), 1662 (2 C=O), 682 (C-S). 1H NMR (DMSO-d6): δ, ppm: 4.41 (s, 2H, CH2), 5.43 (s, 2H, NH2) (D2O exchangeable), 5.88(s, 1H, NNH), 7.14 (t, 1H, H6), 7.31 (d,1H, H5), 7.70 (d, 1H, H8), 7.48 (t, 1H, H7), 8.23 (s, 1H, H3).

Synthesis of α-[(4`-oxoquinazolin-2`-yl) thio] Aceto-3-Substituted Phenyl Hydrazone

To a solution of the hydrazide (4), (0.01 mol, 2.5 g) in absolute ethanol (25 ml), an aromatic aldehyde (0.01 mol) was added with stirring, followed by addition of (1 ml) of glacial acetic acid. The mixture was refluxed for 4 hrs. The reaction mixture was cooled and left in refrigertor for 24 hrs, the resultant precipitate was separate by filtration, washed with cold ethanol then recrystallized from ethanol. The physical properties of compounds (5-12) are illustrated in Table (1), 1HNMR (DMSOd6): δ, ppm: 3.99(s,2H, CH_2), 6.85(d,2H, $H_{3:5}$), 7.42(t,1H, H_6), 7.61(d,1H,

H_8), 7.66(d,2H, $H_{2:6}$), 7.77(t,1H, H_7), 8.07(d,1H, H_5), 8.47(s,1H, CH), 9.68(b,1H, OH), 11.07(s,1H, NH), 12.65(s, 1H, NH) amide

Compd. No.	R	Yield %	m.p. °C	color	IR (neat, ν, Cm^{-1})		
					C=O	N-N	N-H
6	4-hydroxybenzaldehyde	98	244-245	green	1662	1066	3389
7	2-chlorobenzaldehyde	94	110-111	yellow	1676	1079	3368
8	2,4-dichlorobenzaldehyde	95	286-287	green	1670	1057	3358
9	2-piperenal	90	138-139	yellow	1691	1078	3362
10	3-nitrobenzaldehyde	93	212-213	green	1698	1054	3378
11	4-tolualdehyde	98	204-205	green	1681	1082	3362
12	4-N, N-dimethylaminobenzaldehyde	95	215-216	green	1685	1035	3304

Table 1. The physical and IR spectral data of compounds (5-12).

Synthesis of α-[(4`-oxoquinazolin-2`-yl) thio] Acetamido-β-[3``-chloro-4``-Substituted Phenyl Azetidene-2``-One

To a solution of the hydrazone (H95-H104) (0.01 mol) in dimethylformamide (30 ml, triethylamine (0.02 mole, 2.78 ml) was added with stirring followed by dropping wisely addition of chloroactyl chloride (0.02 mol, 1.6 ml) within a period of 30 min. the resulted mixture was refluxed for 10 hrs, then poured on to crushed ice (50 g) to give a precipitate. The precipitate was collected by filtration, washed with cold water, dried then recrystallized from ethyl acetate. The physical properties of compounds (13-20) are illustrated in Table (2). 1H NMR (DMSO-d6): δ, ppm: 3.84(s,2H, CH_2), 5.08(s,1H, NH), 5.44(s,1H, CH), 6.71(d,2H, $H_{3:5}$), 7.05(d,2H, $H_{2:6}$), 7.42(t,1H, H_6), 7.61 (d,1H, H_8), 7.77(t,1H, H_7), 8.07(d,1H, H_5), 9.06(b,1H, OH), 12.65(s,1H, NH) amide.

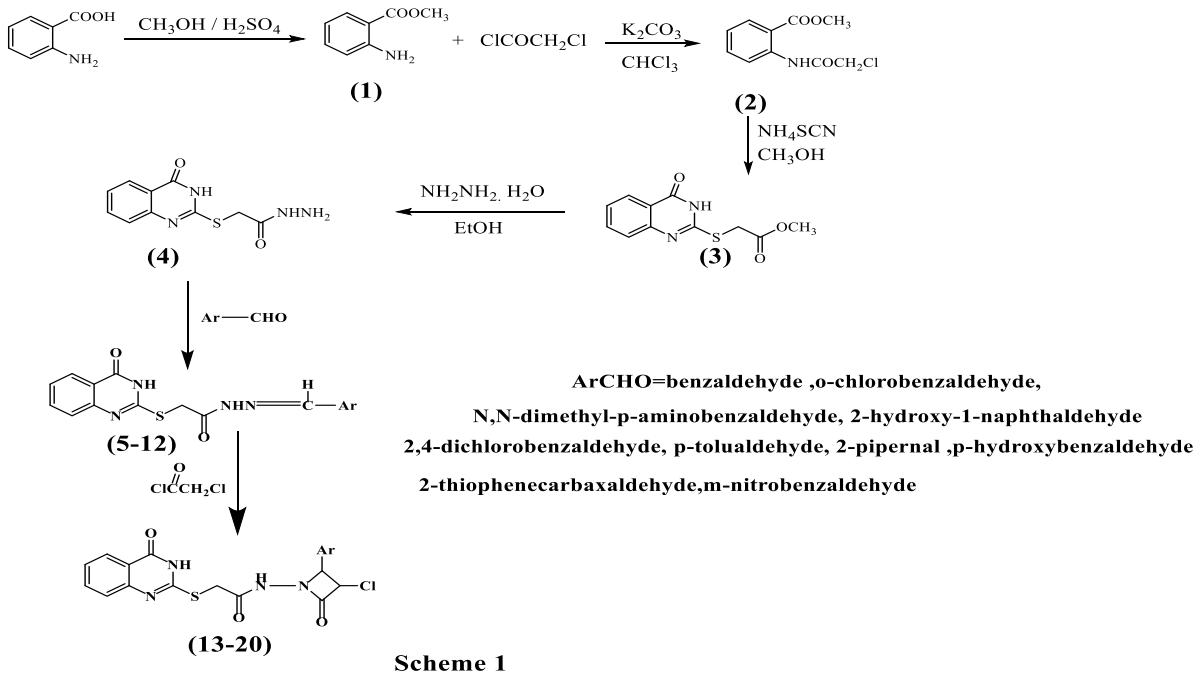
Table 2. The physical and chemical properties of compounds (12-18).

Compd. No.	R'-	Yield %	m.p. ℃	color	IR (neat) , ν (Cm^{-1})			
					C=N	C=O	C-Cl	N-H
13	4-hydroxybenzaldehyde	90	193-194	yellow	1566	1660	732	3365
14	2-chlorobenzaldehyde	88	280-281	yellow	1527	1654	745	3340
15	2,4-dichlorobenzaldehyde	90	209-210	yellow	1578	1686	700	3368
16	2-piperenal	86	246-247	grey	1534	1664	698	3300
17	3-nitrobenzaldehyde	87	235-236	grey	1544	1674	734	3379
18	4-tolualdehyde	91	272-273	grey	1567	1670	750	3354
19	4-N, N-dimethylaminobenzaldehyde	93	286-287	brown	1556	1683	722	3346
20	2-thiophenecarbaxaldehyde	89	256-257	brown	1598	1669	745	3367

Result and Discussion

The synthetic route of the quinazolin-4(3H)-one derivatives (5-7) was illustrated in Figure 1. The primal precursor for these heterocyclic compounds is α-[(4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (4). This compound was synthesized from anthranilic acid via four steps. The anthranilic acid was converted to its methyl ester (1)

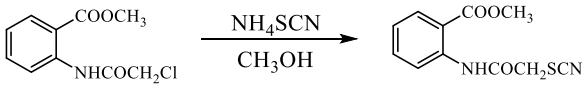
Present as thiol in the solution. The IR spectrum of the hydrazone compound (5) showed absorption bands at 3389 Cm^{-1} for the (N-H) bond stretching quinazolinone and oxadiazole moieties respectively, at 1662for the (C=O) bond stretching and at 1066for the (N-N) bond stretching1HNMR(DMSOd6):δ,ppm:3.99(s,2H,CH_2),6.85(d,2H,$H_{3:5}$) 7.42(t,1H,H_6),7.61(d,1H,H_8),7.66(d,2H,$H_{2:6}$),7.77(t,1H,H_7),8.07(d,1H,H_5),8.47(s,1H,CH),9.68(b,1H,OH),11.07(s,1H ,NH),12.65(s, 1H, NH)amide. Furthermore, two series of derivatives were prepared from the α-[(4`-oxoquinazolin-2`-yl) thio] acetamido-β-[3``-chloro-4``-substituted phenyl azetidene-2``-one. The ester (1) was reacted with chloroacetyl chloride in presence of potassium carbonate as a base to afford methyl 2-(α-chloroacetamino) benzoate (2).



Scheme 1

Figure 1. Through the conventional acid catalyzed esterification method.

The ^{1}H NMR spectrum of compound (2) showed the following chemical shifts (δ, ppm): 3.89 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.27 (t, 1H, H5) , 7.66 (t, 1H, H4), 7.99 (d, 1H, H3), 8.40 (d, 1H, H6), 11.33 (s,1H, NH) [Crews et al, 1998].[16] The reaction of compound (2) with ammonium thiocyanate in absolute ethanol under reflux for 12 h afforded methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (3) via the formation and cyclization of un-isolated methyl 2-(α-thiocyanato acetamino)benzoate (I) as an intermediate compound.



The IR spectrum of the quinazolinone compound (3) showed absorption bands at 3170 $Cm^{-1}$for the N-H bonds stretching of the quinazolinone nucleus, and two absorption bands at 1734, 1682 Cm^{-1} for the C=O bond stretching of the ester and the amide respectively. The proton NMR spectrum of compound (3) showed the following chemical shifts (δ, ppm): 3.69 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 7.4 (t,1H, H6) , 7.75 (t, 1H, H7), 7.98 (d, 1H, H5), 8.23 (d, 1H, H8), 11.14 (s,1H, NH). The ester (3) was converted to the corresponding hydrazide (4) by its refluxing with hydrazine hydrate in absolute ethanol. The absence of the C=O bond stretching of the ester at 1704 Cm^{-1} indicates the full conversion of the ester (3) to the hydrazide (4). The ^{1}H NMR spectrum of the hydrazide (4) (DMSO-d6) showed the following chemical shifts: δ, ppm: 4.41 (s, 2H, CH_2), 5.43 (s, 2H, NH_2) (D_2O exchangeable), 5.88(s, 1H, NNH), 7.14 (t, 1H,H6), 7.31 (d,1H, H5), 7.70 (d, 1H, H8), 7.48 (t, 1H, H7), 8.23 (s, 1H, H3). The hydrazide (4) was used as precursor to synthesize the posterior heterocyclic compounds (5-12). Firstly, the hydrazide (4) was reacted with substituted aldehydes in presence of ethanolic solution to give α-[(4`-oxoquinazolin-2`-yl) thio] aceto-3-substituted phenyl hydrazone (5-12). The first one involves the reaction of compound (5-12) with different aldehydes to synthesize the hydrazones derivatives (5-12). This reaction takes place *via* S_N2 mechanism. These compounds showed an absorption band in the IR spectra at 1662-1691Cm^{-1} for C=O bond stretching, in addition to absorption band at 1704 Cm^{-1} for the ketonic C=O bond stretching related to compound (5), and at 1035-1082 Cm^{-1} for N-N bond stretching. The ^{1}H NMR (DMSO-6d) spectrum of compound (12) showed the following chemical shifts: δ, ppm: 3.84(s,2H,CH_2),5.08(s,1H,NH)5.44(s,1H,CH),6.71(d,2H,$H_{3:5}$),7.05(d,2H,$H_{2:6}$),7.42(t,1H,H_6),7.61 (d,1H,H_8), 7.77(t,1H,H_7),8.07(d,1H,H_5),9.06(b,1H,OH),12.65(s,1H,NH)amide.The ^{1}H NMR (DMSO-6d) spectrum of compound (14) showed the following chemical shifts: δ, ppm: 1.24 (d, 2H, allelic CH_2), 3.90 (s, 2H, CH_2), 4.09 (d, 1H, vinylic CH), 6.1 (d, 2H, vinylic CH_2), 7.37 (t, 1H, H6), 7.48 (t,1H, H7), 7.47 (d, 1H, H5), 7.83 (d, 1H, H8), 8.19 (s, 1H, H3). The ^{1}H NMR (DMSO-6d) spectrum of compound (10) showed the following chemical shifts: δ,

ppm: 3.18 (s, 2H, benzylic CH_2), 3.86 (s, 2H, CH_2), 7.39 (t, 1H, H6), 7.46 (t, 1H, H7), 7.48 (d, 1H, H5), 7.71(d, 1H, H8), 7.81-8.21 (m, 5H, benzylic-H), 8.26 (d, 1H, H3). The second series involves the reaction of compound (5) with different aldehydes to synthesize the azetidenes derivatives (13-20). These compounds showed an absorption bands in their IR spectra at 1654-1689 Cm^{-1} for C=O bond stretching, at 1527-1598 Cm^{-1} for C=N bond stretching, at 698-750 Cm^{-1} related to C-Cl bond stretching and at 3300-3379 Cm^{-1} for the N-H bond stretching. The ^1H NMR (DMSO-6d) spectrum of compound (13) showed the following chemical shifts: δ, ppm:3.84(s,2H, CH_2), 5.08(s,1H, NH), 5.44(s,1H, CH), 6.71(d,2H, $H_{3:5}$), 7.05(d,2H, $H_{2:6}$), 7.42(t,1H, H_6), 7.61(d,1H, H_8), 7.77(t,1H, H_7), 8.07(d,1H, H_5), 9.06(b,1H, OH), 12.65(s,1H, NH) amide. The ^1H NMR (DMSO-6d) spectrum of compound (14) showed the following chemical shifts: δ, ppm: 3.84(s,2H, CH_2), 5.08(s,1H, NH), 5.44(s,1H, CH), 7.21(t,1H, H_5), 7.22(d,1H, H_6), 7.25 (t,1H, H_4), 7.42(t,1H, H_6), 7.61 (d,1H, H_8), 7.68 (d,1H, H_3), 7.77(t,1H, H_7), 8.07(d,1H, H_5), 12.65(s,1H, NH) amide. The ^1H NMR (DMSO-6d) spectrum of compound (17) showed the following chemical shifts: δ, ppm: 3.84(s,2H, CH_2), 5.08 (s,1H, NH), 5.44(s,1H, CH), 7.42(t,1H, H_6), 7.61(d,1H, H_8), 7.64(t,1H, H_5), 7.76(d,1H, H_6), 7.77(t,1H, H_7), 8.07(d,1H, H_5), 8.16(d,1H, H_4), 8.22(s,1H, H_2), 12.65(s,1H, NH) amide**.**

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

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Author Information

Hiba Amen AL-ALAAF University of Mosul, Department of Chemistry, Mosul/Iraq
Contact E-mail: hibaalaf80@gmail.com

Mohammed A. AL-IRAQI
College Al-Noor University
Bartella, Irak

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